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(71)(72) Applicants and Inventors: KANAKARIS, Panagiotis [GR/GR]; 33 Koletti Street, GR-106 77 Athens (GR). KAROUZAKIS, Petros [GR/GR]; 9 Bakou Street, GR-115 24 Athens (GR).

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(54) Title: USE OF MISOPROSTOL OR/AND MISOPROSTOL ACID FOR PREPARING DRUG IN ORDER TO CURE ERECTILE DYSFUNCTION

(57) **Abstract**

The invention relates to using an already known pharmaceutical substance, misoprostol or/and its first metabolite (misoprostol acid) whose structural formulas are presented in pages 3 and 5 (Figures I and II), for preparing a drug of external use destined: a) to cure erectile dysfunction and b) as accessory means in the diagnosis of erectile dysfunction. Misoprostol or/and misoprostol acid according to the described method are applied externally on the glans of the penis, the prepuce and the urethra, are absorbed and cause topical vasodilation resulting in a hard and durable erection for patients suffering from disorders of erection, due to vascular or other causes.

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USE OF MISOPROSTOL OR/AND MISOPROSTOL ACID FOR PREPARING DRUG IN ORDER TO CURE ERECTILE DYSFUNCTION

The invention relates to the use of an already known pharmaceutical substance, misoprostol as well as its first metabolite, misoprostol acid, for the preparation of a drug for external use which is destined to cure erectile dysfunction. Nowadays the pharmaceutical treatment of erectile dysfunction -except of the cases of hormonal insufficiency, which are generally rare and in which a suitable substitution therapy is followed-includes mainly the use of intracavernosous injections consisting in the direct injection of vasodilatory drugs (papaverine, phentolamine and alprostadil) into the corpora cavernosa of the penis (Campell's Urology, ed. W. B. Saunders Company, 6th edition, volume III, p. 3055-3057). Although this method is the most efficient and perhaps the only scientifically acceptable, it has the serious disadvantage of the form (injection) as well as the manner of administration intracavernosal.

Yohimbin, an a_2-adrenergic inhibitor, is administrated per os, however the efficiency of this old method is doubtful (Campell's Urology, ed. W. B. Saunders Company, 6th edition, volume III, p. 3053).

In former times the topical application of a nitroglycerin paste had been proposed (Claes et al 1989), but the method was not therapeutically applied because of doubtful efficiency and serious side-effects (Campell's Urology, ed. W. B. Saunders Company, 6th edition, volume III, p. 3053).

The topical application of prostaglandin E_1 (or alprostadil)

in the form of an endourethral gel or stick as a means of limited efficiency in the therapy of male impotence of a vascular cause (International Journal of Impotence Research, Stocton ed., vol. 7, September 1995, supplement I, p. 05-06) was recently proposed, we must note that the discovery of vasodilatory drugs with sufficient transcutaneous absorption or the use of methods (e.g. ionophoresis) which can reinforce the penetration of such drugs through the skin of the mucosal membranes, inside the corpora cavernosa of the penis has for long attracted the interest of many research workers (Campell's Urology, ed. W. B. Saunders Company, 6th ed., vol. III, p. 3057)

Up to day a common denominator of the methods destined for external application is mainly the low efficiency combined with increased therapy cost and the apparition of more or less serious side-effects.

The present method aims at the removal of the drawbacks of the above methods using misoprostol in the symptom therapy of male impotency. Misoprostol is the general name of a synthetic prostaglandin belonging to the E_1 series (PGE_1 analogs).

Synthesis: P. W. Collins, R. Pappo, Belgian patent 827.127, American patent 3.965.143 (The Merck Index, ed. Merck & Co. Inc, 11th edition, 1989, p. 6128).

Its chemical name is (11a, 13E)-(±)-11, 16-Dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester or (±)-(methyl)-(1R, 2R, 3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate or (±)-15-deoxy-(16RS)-16-hydroxy-16-methyl-PGE_1 methyl ester.

It is consisted of 4 stereoisomers in about equal proportions [(+)&(-) enantiomers of 16R- and 16S-forms]. (The Merck Index, 11th edition, 1989, p. 6128). The empirical formula is $C_{22}H_{38}O_5$. Its structural formula appears in Fig. I.

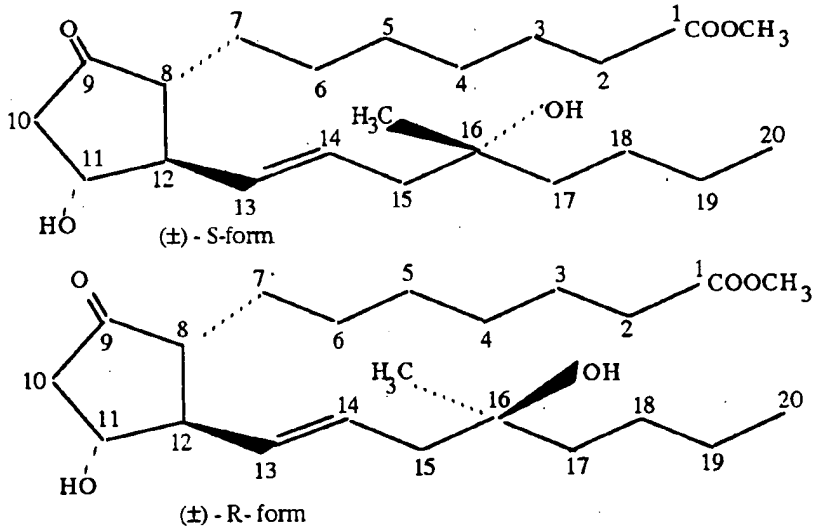

Figure I.

Compared with other prostaglandins of group E_1 and especially alprostadil, misoprostol bears a methyl group ($-CH_3$) on the carbon atom of position 16.

According to a method which relates the biological action of various medicament molecules to its chemical structure (Method of Minimum Stereochemical Difference, "Planning of drugs", P. Kourounakis-E. Rekka, ed. Graphical Arts, Thessaloniki, 1992, p. 152) it appears that due to this group we have a big penetration of misoprostol in the underlying tissues and a local vasodilation which cures erection dysfunctions. Misoprostol is used today orally as

antiulcer drug (Physicians Desc Reference, PDR, ed. Medical Economics Data, Production Company at Montrale 48th edition, 1994, P. 2197-2199).

In particular it is administered for the prevention of gastric ulcer to patients who take non-steroid antiinflammatory drugs. It is available in the countries of Europe and U. S. A. by Searle Company under the commercial name Cytotec®. In none country is the drug mentioned as suitable for male impotence nor are there any relevant reports on the international bibliography. On a contrary amongst the undesirable effects in oral therapy with misoprostol is male impotence (Physicians Desc Reference, ed. Medical Economics Data, Production Company at Montrale, 48th edition, 1994, p. 2197-2199).

In spite of the fact that misoprostol exerts reduced vasodilatory action compared with alprostadil when administered intracanernously, it creates a stronger local vasodilation and consequently greater increase in blood flux when applied externally to the penis and the urethral mucosa. Due to the topical vasodilation we have a sufficiently long and durable erection. On the other hand due to the fact that the degree of response to a small dose of misoprostol (durability and hardness of erection) depends on the physiological condition and function of the penile vessels, misoprostol can be used as accessory diagnostic means (instead of papaverine or alprostadil) in the "Doppler" method or the cavernosometry, for the determination of the extent and kind of vascular damage (about the use of

vasodilatory drugs as accessory diagnostic means in the "Doppler" method or cavernosometry, see Erektile Impotenz, ed. Enke, p. 68-77 & p. 88-110).

Equally strong topical vasodilatory action after external application is exerted by the hydrolysis product of misoprostol, (misoprostol acid) which anyway constitutes the first misoprostol metabolite after its introduction in the organism (see Fig. II).

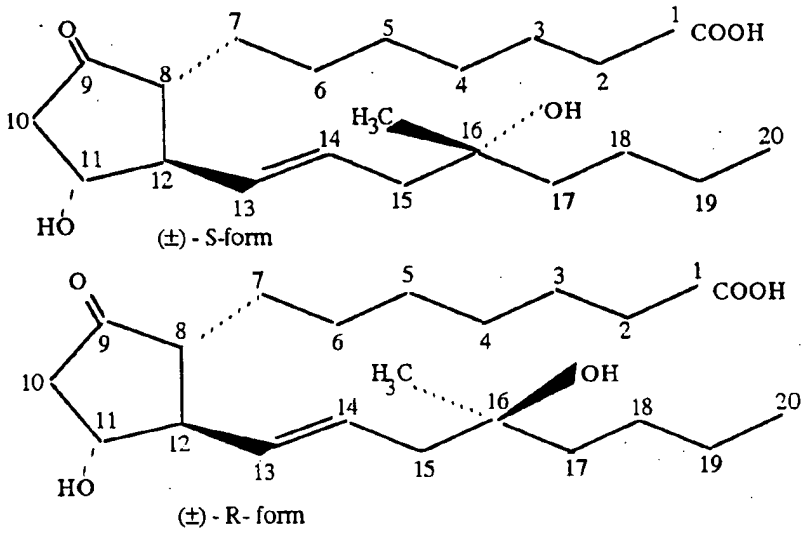

Figure II.

Last because of the intense topical vasodilatory action of misoprostol and the corresponding free acid, the two pharmaceutical molecules reinforce the absorption of other vasoactive substances (e.g. alprostadil) resulting in the occurrence of synergic action.

Misoprostol can be dissolved in water and its compatibility with excipients provides the opportunity of production of a

variety of simple pharmacotechnical forms for external use, which are at the same time very well tolerated by the skin and the mucousa. From the above mentioned description it appears that the most serious advantage of the method is the manner of administration of the drug (external in combination with the lack of undesirable action in the suggested doses or/and the proposed pharmacotechnical forms) the relatively low cost and especially the most satisfactory result together with corresponding methods.

Amongst the probable methods of application, most advantageous is a synthesis in the gel form of relatively low viscosity which contains 0,9 % w/v misoprostol in the methylform of methylester and/or free acid, a complexforming means, as 1,6% w/v a-cyclodextrine and substances suitable for the formation of a gel e.g. hydroxypropyl methylcellulose "3000" 2% w/v, propylene glycol 10% v/v and Water to 100 ml. The gel contains 9 mg of active substance per ml.

Method of application: 0,1-0,25 ml (or more, depending on responce) are pasted or spread on the glans of penis.

9 examples related to the pharmacotechnical forms and the ways of application of misorostol:

1)0,05-0,20 ml gel, relatively low viscosity containing 0,9% w/v misoprostol to apply on the glans of the penis or on the prepuce.

Synthesis:

1-1. Misoprostol	0,9 g
Hydroxypropyl Methylcellulose "3000"	2 g
Water purified to	100 ml

1-2. Misoprostol	0,9 g
Sodium Carboxymethylcellulose	2 g
Propylene Glycol	25 ml
Water purified to	100 ml

2)0,05-0,20 ml gel of relatively high viscosity, containing 0,50% w/v in misoprostol for endourethral application at a depth 2-5 cm from the outside urethra opening.

Synthesis:

2-1. Misoprostol	0,50 g
Hydroxypropyl Methylcellulose "3000"	4 g
Water purified to	100 ml
2-2. Misoprostol	0,50 g
Sodium Carboxymethylcellulose	4 g
Propylene Glycol	25 ml
Water purified to	100 ml

3)0,05-0,20 ml of aqueous solution of misoprostol containing 0,9% w/v for spreading on the glans of the penis or of the prepuce. The solution can also contain propylene glycol or glycerol in the corresponding proportions (e.g. 10%) to increase the viscosity of the solution.

4)0,05-0,20 ml of ointment or emulsion of containing 0,9% w/w misoprostol for apply on the glans of the penis or on the prepuce, where misoprostol is found spread in the continuous (aqueous) phase.

Synthesis:

4-1. Misoprostol	0,9 g
Vanishing Cream to	100 g

(Although for the requirements of this example as Vanishing

Cream we used Bepanthéne® Cream of Roche, we have various creams o/w which are available in commerce or are described in National Pharmacopoeies and can be used for the same purpose).

5) Endourethral sticks of suitable dimensions, weight about 500 mg, containing 0,04-0,20% w/w misoprostol to apply on the urethral mucosa.

Synthesis:

5-1. Misoprostol	0,04-0,20 g
Glycerol	70 g
Gelatine	20 g
Water purified to	100 g

6) 0,05-0,25 ml gel (or more depending of response) according to the examples (1-1) and (2-1) which contains moreover 1,6% w/v a-cyclodextrine.

7) 0,05-0,25 ml gel (or more depending of response) according to the example (6) which contains moreover 10 ml ethyl alcohol 96° and 0,5 mg/ml alprostadil.

Notes: 1) The incorporation of misoprostol in bases already mentioned took place in normal temperature (20-25°C) and at a temperature not exceeding 40°C.

2) No significant changes in misoprostol activity was observed as a function of pH, we observent however an important reduction or/and neutralization of misoprostol action in the presence of Polysorbate "80".

3) The time of appearance of the result varies from 20-40 minutes. The timing of the appearance and the intensity of the result seems to be able been positively influenced by certain

moisturising agents (e. g. Propylene Glycol, Glycerol) as well as by certain substances which reinforce by various mechanisms the transcutaneous absorption (e. g. Urea, Acid Citric).

High once only doses of misoprostol (>1800 mcg on the glans of the penis and >1000 mcg in the urethra) cause certain systematic undesirable effects as shudder, feeling of hard ship, excitement and diarrhea. The presence of a-cycodextrine reduces the undesirable effects and allows the application once only of higher doses (>2000 mcg) without notable effect on the timing of its action but with positive effect on the intensity result and with prolonging of its duration.

5)The doses which are mentioned in the examples are only indicative since the intensity of the result depends, apart from the nature and the grade of the erection dysfunction on other factors as e. g. the degree of moisturising of the underlying tissue, the physiological situation of the skin or the mucosa etc. As had already been mentioned, misoprostol is an extremely hydrophile molecule compared with other prostaglandins of E_1 series (e. g. with alprostadil which can be dissolved in alcohol but her solubility in water is only 8000 mcg/100 ml at 35°C).

This consists an important advantage:

a)Because no use of organic factors is required (e. g. ethyl alcohol) which usually irritate tissues and are thus unsuitable for application on the skin and especially the mucus.

b)Because it allows the incorporation of active substances

on a very small amount of excipient, suitable for application on surfaces of limited extent, as e. g. the urethra or the glans of the penis.

6)Because of the described irritation of the uterine fibbers (Physicians Desc Reference, ed. Medical Economics Data, Production Company at Montrale, 48th edition, 1994, p. 2197-2199) misoprostol must not contact the female genital apparatus.

Claims

1)The use of misoprostol or/and its first metabolite, misoprostol acid, for the production of a drug applied topically on the glans of the penis, the prepuce or the urethra and is destined:

a)For the symptomatic therapy of male impotence due to vascular or other causes and

b)As aid in the diagnosis of erection dysfunction.

2)The use of misoprostol and/or its metabolite (misoprostol acid) according to claim (1) either as racemic mixtures or in the form of one of the stereoisomers from which they consist: [(±)-R form & (±)-S form].

3)The use of misoprostol and misoprostol acid according to claims (1) and (2) in the form of various galenic preparations (solutions, ointments, endourethral sticks, systems of controlled transdermal absorption) which, according to the general principles of pharmacotechnics, facilitate the application and precise administration of the right doses for the achievement of the desired therapeutical or diagnostic aim as described in claim (1).

4)The use of misoprostol and misoprostol acid according to claim (1), (2) and (3) in combination with other vasodilatory drugs as alprostadil for the appearance of synergistic action, as well as "passage accelerators" used normally in pharmaceutical technology aiming to increase absorption of drugs through the skin or the mucosa.

5)Use of misoprostol and misoprostol acid according to claim (1), (2) and (3) in combination with a-cyclodextrin or other

substances which, according to the general methods used in pharmacology impedes or retards the appearance or undesired effects of the drug or prolong their pharmaceutical action.

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/GR 98/00012

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANON.: "Alprostadil for erectile impotence." DRUG AND THERAP. BULL., vol. 33, no. 8, 1995, pages 61-62, XP002049460	
A	US 5 510 384 A (MCKEE ET AL.) 23 April 1996	
A	WO 93 00894 A (SCOTT) 21 January 1993	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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